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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,849	06/27/2002	William Hugold Velander	TRANS 1	2472

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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,849	VELANDER, WILLIAM HUGOLD	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *1,5-8,11-13,16,17,20,22,24,25,27 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *28-31,33,35,36,38,40-44,46,48,50 and 55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08). Paper No(s)/Mail Date *10/11/02 (2pages)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,5-8,11-13,16,17,22,24,25,27-31,33,35,36,38,40-44,46,48,50,53 and 55.

This Application, filed June 27, 2002, is a 371 of PCT/US00/22616 filed August 18, 2000, and claims priority to U.S. Application 60/149,936 filed August 19, 1999.

Claims 1, 5-8, 11-13, 16, 17, 22, 24, 25, 27-31, 33, 35, 36, 38, 40-44, 46, 48, 50, 53, 55 are pending.

Election/Restrictions

Applicant's election with traverse of Group II in the reply filed on November 17, 2004 is acknowledged. The traversal is on the ground(s) that Groups I and II have unity of invention because they recite a shared or corresponding technical feature having a contribution over the prior art. This is not found persuasive because as stated in the Restriction Requirement (page 3, point 6) "according to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art." The invention lacks unity because the technical feature, prothrombin, is well known in the art. For this reason, the composition comprising prothrombin and thrombin have been restricted from a transgenic animal that produces prothrombin and thrombin.

The Applicant points out that the Examiner must show, absent a restriction, that there is an undue search burden (Applicant's Response to Restriction Requirement, page 2, second paragraph). However, for purposes of 371 restriction, restriction is carried out according to 371 practice, and not according to U.S. practice, wherein the Examiner must demonstrate undue search burden. Had this been restricted according to U.S. practice, the restriction would stand because Group I is to a transgenic animal

that produces prothrombin or thrombin and Group II is to thrombin, prothrombin, and a composition comprising prothrombin/thrombin. Group I is an animal, classified in class 800, subclass 13, and Group II is a protein, classified in class 530, subclass 350+. These are two materially different inventions, requiring different areas of search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 5-8, 11-13, 16, 17, 20, 22, 24, 25, 27, 53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 17, 2004. Claims 28-31, 33, 35, 36, 38, 40-44, 46, 48, 50, 55 are under consideration in this Office Action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28, 40, 50 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19, 26 of copending Application No. 10/062,447. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 28, 40, 50 are broad for a "thrombin-related polypeptide," of which Factor IX of Application '447, is encompassed. In this situation, "thrombin-related polypeptide" has been interpreted to mean any polypeptide involved in the blood-clotting cascade.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section

351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 28, 40, 50 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 10/062,447 which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application. Claims 28, 40, 50 of the instant Application are to a prothrombin or prothrombin-related polypeptide isolated from a transgenic organism, to a composition comprising a prothrombin or prothrombin-related polypeptide produced in a transgenic organism, and to a composition according to claim 40, wherein the prothrombin or prothrombin-related polypeptide is produced in milk of a non-human transgenic female mammal. Claims 19 and 26 of Application '447 are to a purified biologically active human Factor IX produced in a transgenic pig and to milk of a transgenic pig comprising biologically active human Factor IX produced in a transgenic pig. The instant Application claims are to a "prothrombin-related polypeptide." "Related" has been broadly interpreted to encompass proteins encompassed in the blood-clotting cascade.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. This

rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

Claims 28, 29, 30, 33, 35, 36, 38, 40, 41, 42, 44, 46, 48, 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Holly and Foster (U.S. Patent Number 5,476,777, patented December 19, 1995).

Claims 28, 29, 30, 33, 35, 36, 38 are to a prothrombin or prothrombin-related polypeptide isolated from a transgenic organism, wherein the prothrombin or prothrombin-related polypeptide comprises a region having an amino acid sequence 80%-100% identical to that of a mammalian or human thrombin or prothrombin and that the prothrombin or prothrombin-related polypeptide differs in its post-translational modification from naturally occurring prothrombin polypeptides. These modifications may differ from naturally occurring prothrombins in any one or combination of its glycosylation, γ-carboxylation or activation proteolytic processing. Claims 40, 41, 42, 44, 46, 48, 55 are to a composition comprising a prothrombin or prothrombin-related polypeptide produced in a transgenic organism, wherein the prothrombin or prothrombin-related polypeptide comprises a region having an amino acid sequence 80%-100% identical to that of a mammalian or human thrombin or prothrombin. Claim 55 is to a method for producing a prothromin or a prothrombin-related polypeptide comprising expressing the prothrombin or prothrombin-related polypeptide in a transgenic organism and isolating from the transgenic organism the prothrombin or prothrombin-related polypeptide and that the prothrombin or prothrombin-related

polypeptide differs in its post-translational modification from naturally occurring prothrombin polypeptides. These modifications may differ from naturally occurring prothrombins in any one or combination of its glycosylation, γ-carboxylation or activation proteolytic processing.

Holly and Foster teach the construction of two prothrombin expression plasmids and demonstrate their expression in yeast cells (Example 5). Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972)

The first construct, pZH10, comprised a DNA molecule encoding a thrombin precursor comprising Kringle 2, A chain and serine protease domains of human prothrombin was constructed (column 25, lines 18-26). The second construct, pZH8, comprised a DNA molecule encoding a thrombin precursor comprising Kringle 1, Kringle 2, the A chain and the serine protease domain of human prothrombin (column 27, lines 23-30). pZH10 and PZH8 were transformed into *Saccharomyces cerevisiae* strains

ZM114 and ZM118 and transformants were selected for their ability to grow in the presence of glucose as the sole carbon source (column 28, lines 1-12). Selected transformats were assayed for their ability to produce activatable thrombin by inoculating a 5ml over YEPD culture of each transformant into 1.2L YEPD+6% glucose in a 2.5L flask and incubating the cultures for 60 hours at 30°C in a shaker. 100ml samples were taken at 24, 36, 48, and 60 hours post inoculation. The samples were centrifuged and the spent medium assayed for the presence of activated thrombin in a chromogenic assay (column 28, lines 13-20). To each 20ul sample of supernatant, 80ul of 1ug/ml of snake venom activator diluted in activation buffer was added. The samples were incubated a 37°C for one hour. After incubation, 100ul of 0.25mM thrombin chromogenic substrate was added and the plates were allowed to incubate for one to three hours to allow for color development (column 28, lines 28-40). Holly and Foster teach that at 48 hours, ZM118 cells transformed with pZH8 produced 5 mg/ml of activatable thrombin, ZM118 cells transformed with pZH10 produced 02.ug/ml of activatable thrombin, ZM114 cells transformed with pZH8 produced 0.84ug/ml of activatable thrombin, and ZM114 cells transformed with pZH10 produced 0.18ug/ml of thrombin (column 28, table 3).

Holly and Foster anticipate claims 28, 29, 30, 33, 35, 36, 38, 40, 41, 42, 44, 46, 48, 55 because they teach that human prothrombin or prothrombin-related polypeptides were produced by transgenic yeast. The yeast taught by Holly and Foster are considered to be transgenic as "transgenic" has been defined by the American Heritage dictionary as, "of, relating to, or being an organism whose genome has been altered by

the transfer of a gene or genes from another species or breed: *transgenic mice; transgenic plants.*" "Composition" is defined by the Merriam-Webster online dictionary as, "**1 a :** the act or process of composing: *specifically* **:** arrangement into specific proportion or relation and especially into artistic form **b** (1) **:** the arrangement of type for printing <hand *composition*> (2) **:** the production of type or typographic characters (as in photocomposition) arranged for printing; **2 a :** the manner in which something is composed **b :** general makeup <the changing ethnic *composition* of the city -- Leonard Buder> **c :** the qualitative and quantitative makeup of a chemical compound; **3 :** mutual settlement or agreement; **4 :** a product of mixing or combining various elements or ingredients; **5 :** an intellectual creation: as **a :** a piece of writing; *especially* **:** a school exercise in the form of a brief essay **b :** a written piece of music especially of considerable size and complexity; **6 :** the quality or state of being compound; **7 :** the operation of forming a composite function."

Based on this definition, Holly and Foster demonstrate compositions comprising a prothrombin or prothrombin-related polypeptide. One example is a yeast expressing prothrombin. Another example is the chromogenic assay solution, wherein each 20ul sample of supernatant, 80ul of 1ug/ml of snake venom activator diluted in activation buffer was added. Following incubation, thrombin chromogenic substrate was added (column 28, lines 40-51). Holly and Foster also demonstrate a prothrombin or prothrombin-related polypeptide isolated from a transgenic yeast that differs in its post-translational modification from naturally occurring prothrombin polypeptides. The yeast

constructs PZH10 and PZH8 do not contain the Gla domain, the domain that contains γ-carboxyglutamate residues.

Thus, Holly and Foster anticipate claims 28, 29, 30, 33, 35, 36, 38, 40, 41, 42, 44, 46, 48, 55.

Claims 28, 29, 30, 40, 41, 42, 50, 55 rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (1996, Thrombosis Research, 82:225-234).

Lee et al. teach the isolation of human Protein C (HPC), a protein related to prothrombin. Lee et al. teach the construction of the hybrid gene containing the mouse whey acidic protein gene and HPC cDNA, which was used to express HPC in milk of swine. Recombinant HPC was purified by selective precipitation and ion exchange column chromatography (page 226, paragraph headed, "Transgenic swine, purified rHPC and activated rHPC(rAPC)"). Lee et al. teach that Protac, a glycoprotein from the venom of the Southern Copperhead (Agkistrodon contortrix) snake forms a Protac/Protein C complex (page 227, first paragraph under Results). This form of processing differs from the post-translation modification of thrombin and prothrombin. Thus, Lee et al. anticipate claims 28, 29, 30, 40, 41, 42, 50, 55.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-

272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, Ph.D. can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH